Remarks

Claims 1-2, 4-5 and 25-30 are pending in the present application, claims 10-24 having been cancelled previously *without prejudice* pursuant to the Examiner's restriction requirement and Applicant's decision to elect with traverse to prosecute the invention of original claims 1-9. Upon the indication of allowable subject matter, and before the issuance of any patent from this application, Applicant will give consideration to filing a divisional application for the claimed subject matter previously cancelled. The amendments to the claims have been made to indicate that the present methods are directed to the use of noribogaine as a non-addictive analgesic agent to treat pain in a patient which is treatable with an addictive opioid analgesic such as morphine. Support for the amendments to the claims can be found throughout the originally filed application and claims and in particular, at page 3, second full paragraph, page 6, first paragraph and in particular, lines 4-5, and on page 9 in the examples section and in particular in the last paragraph at lines 20-23. Support for the amendment to claim 6 can be found in the specification at page 3, in line 6. No new matter has been added by way of the present amendment.

The Examiner has withdrawn all of the previously stated rejections of the claims filed with the amendment of October 25, 2004. In this office action, the Examiner has rejected the previously submitted claims variously under 35 U.S.C. §112, first pargraph, 35 U.S.C. §102(e) and §103 for the reasons which are stated in the January 12, 2005 office action. For the reasons which are presented hereinbelow, it is respectfully submitted that the amended claims address all of the Examiner's rejections and the claims are now in condition for allowance.

The §112, First Paragraph Rejection

The Examiner has rejected claims 6 and 9 under 35 U.S.C. §112, first paragraph for the reasons which are stated in the office action on pages 4-8. In sum, the Examiner has rejected those claims because they read on a body of opioid antagonists which are unknown and therefore the claims 6 and 9 can only be practiced using undue experimentation. Applicants traverse the Examiner's rejection inasmuch as claims 6 and 9 are clearly enabled.

In making her rejection that claims 6 and 9 are non-enabled, the Examiner contends that the term opioid antagonist is non-enabled because the use of the term may embrace certain antagonists which are unknown and trying to find unknown opioid antagonists requires undue experimentation. Applicants respectfully traverse the Examiner's rejection.

Claims 6 and 9 of the present application are directed to the use of noribogaine and an opioid antagonist for the treatment of pain which is treatable with an opioid agonist analgesic. Claim 9 is directed to the method of claim 9 wherein the noribogaine and the opioid antagonist are administered transdermally. By the plain meaning of this claim, one of ordinary skill can readily practice this invention without undue experimentation because one can administer noribogaine and any number of opioid antagonists to produce the intended results which are directed to the treatment of pain The term opioid antagonist is one which is well known in the art and the routineer can readily pick and choose from a number of opioid antagonists specifically set forth in the specification to combine with noribogaine in treating pain according to the present invention. Indeed, opiate receptors were first described in the 1970's so there has been more than three decades of scientific information and practice related to these receptors and in particular, to opioid (receptor) antagonists. There is no absolutely no undue experimentation which has to be utilized for the routineer to make and use the present invention.

The Examiner is not arguing that the present claims 6 and 9 are non-enabled *per se*, but rather that the use of the term opioid antagonist is so broad as to encompass compounds which may be opioid antagonists but which are presently unknown because they have yet to be discovered. Consequently, the Examiner has taken the position that the term opioid antagonist, although a term directed to well-known compounds and generally practiced without undue experimentation, embraces future unknown opioid antagonists, and because the person of ordinary skill cannot be seen to have a crystal ball obviously doesn't know of all future compounds which are opioid antagonists and consequently the use of this term is necessarily overbroad, thus rendering the invention of claims 6 and 9 non-enabling. It is respectfully submitted that the Examiner's argument should be withdrawn because it flies in the face of current chemical patent practice and negates a good body of existing patent law.

It is respectfully submitted that although well-intentioned, the Examiner is misapplying

the law on this issue, because to accept the Examiner's rejection and analysis would be to negate more than 100 years of well-settled patent law and invalidate literally hundreds of thousands of issued patents in one fell swoop. In particular, the undersigned attorney has searched the electronic records of the United States Patent and Trademark office and found literally scores of patents which use the term opioid, opiate antagonist or opiate agonist generically in a claim. We have enclosed four exemplary patents for the Examiner's review. These are U.S. no. 6,451,806 (claims 1, 25, 31 and 35); 6,806,291 (claims 5 and 13) ; 6,864,271 (claims 1, 2, 14, 16); and 6,865,444 (claims 11 and 22). Notwithstanding the legal arguments which are presented below, if the Examiner's argument is to be accepted as law, all claims making use of such generic terms would be invalid. Thus, in concept, the claims of literally hundreds of thousands of patents would be invalid, even though the patent office has determined those same claims to be enabled and invalid. The Examiner should withdraw this rejection.

The term used in claims 6 and 9, "opiate antagonist" means just that- an antagonist of an opiate or an inhibitor of the action of an opiate analgesic such as morphine. This is a term which is well-known in the art and has been used for a number of years to describe compounds which fall under that definition. One of ordinary skill understands the term, can readily identify compounds which fall under that term and by application of routine techniques can pick and choose opiate antagonists to use in the present invention. None of this represents undue experimentation. Practice of claims 6 and 9 does not represent undue experimentation.

In re Bowen, 181 USPQ 48 (CCPA 1974), copy enclosed, is instructive here. This decision involved chmical reactions which were recognized as having a high degree of unpredictability. Yet in Bowen, the Court reversed the Board's non-enablement rejection where the claims contemplated numerous polymers in addition to the ones specifically described in the applicant's specification, because no reason was given why the claims did not realistically enable one of ordinary skill in the art to practice the invention. The same can be said here. In fact, if anything, the present claims represent an even stronger case of enablement than did the specification in In re Bowen, because in Bowen the use of the objected to term required at least further identification of polymers in addition to the single species described in the specification, whereas in the present specification, an opioid antagonist is well known in the art and primarily can be identified by simply looking those compounds up in a

reference which describes opioid antagonists. Thus, the present specification can be readily supplemented without engaging in *any* experimentation, let alone *undue* experimentation. As to the Examiner's argument that the term opioid antagonist in claims 6 and 9 of the present application embraces future, unknowable embodiments of opioid antagonists, the CAFC had this to say in SRI International v. Matsushita Electric Corp. of America and Matsushita Electric Industrial Co., Ltd., 775 F.2d 1107; 227 U.S.P.Q. 577:

> The law does not require the impossible. Hence, it does not require that an applicant describe in his specification every conceivable and possible future embodiment of his invention. The law recognizes that patent specifications are written for those skilled in the art and requires only that the inventor describe the "best mode" known at the time to him of making and using the invention.

Id. at page 20, see enclosed copy.

Thus, it is respectfully submitted that claims 6 and 9 meet the requirements of 35 U.S.C. §112, first paragraph, and Applicant's claims clearly meet the requirements of the law. Applicants respectfully request the Examiner to withdraw her rejection of claims 6 and 9 under 35 U.S.C. §112, first paragraph.

The §102(e) Rejection

The Examiner has rejected the previously filed claims under 35 U.S.C. §102(e) as being anticipated by Olney (US patent no. 5,925,634). The Examiner recognizes that Olney discloses the use of ibogaine in the treatment of *neuropathic* pain. Given that Olney teaches the use of ibogaine to treat neuropathic pain and noribogaine is a metabolite of ibogaine, the Examiner concludes that the present claims are anticipated and therefore, unpatentable. Applicants respectfully traverse the Examiner's rejection.

As amended, the claims are directed to the use of noribogaine for the treatment of pain which is treatable with an opioid agonist analgesic, for example morphine, without addiction as set forth in the claims of the present application. The present invention relates to the unexpected finding that noribogaine, a metabolite of ibogaine, acts to alleviate pain in a patient

by acting on the same receptors acted on by opioid agonists such as morphine, i.e., the μ receptor. Thus, the present invention relates to the discovery that noribogaine is a non-addictive μ receptor agonist. Olney, in complete contast to the present invention, discloses the use of ibogaine as an NMDA antagonist for the treatment of *neuropathic* pain, which is pain which is mediated through NMDA receptors, not μ receptors as in the case of the present invention.

That Olney clearly does not anticipate the present invention is found in Olney's disclosure in the abstract on the first page of the patent. That Abstract in Olney states:

> This invention discloses that ibogaine, a plant derivative, can be used safely to treat neuropathic pain *(i.e., pain which does not respond conventionally to opiate drugs such as morphine).* Emphasis ours. See the first four lines of the Olney abstract.

Thus, Olney clearly does not teach the use of ibogaine for use as a substitute for an addictive opioid agonist such as morphine because Olney recognized (as the art recognized), that ibogaine did not act at the receptors at which opioid agonists acted (i.e., μ receptors). Rather, Olney teaches the use of ibogaine to treat neuropathic pain which is mediated through NMDA receptors by functioning as an antagonist of the NMDA receptor. Because the present claims are directed to the treatment of pain mediated through μ receptors, not NMDA receptors, no anticipation of the present invention by Olney is made out. Indeed, Olney clearly teaches away from the present invention.

As further evidence, Applicants point to the present specification and in particular, the examples on page 9 and 10, which evidences that noribogaine is a potent full μ receptor agonist, whereas ibogaine evidenced extremely weak activity, even at high concentrations above 100 μM. (more than 300 fold greater than the noribogaine used). Thus, ibogaine is not even useful in the present invention. As further evidence of the distinction between the present invention and the Olney disclosure is the fact that noribogaine is much less active than is ibogaine in binding to the NMDA receptor. See, the enclosed paper of Mash, et al., *Neurosciences Letters,* 192, 53-56 (1995). Thus, Olney teaches one of ordinary skill away from using ibogaine to treat pain otherwise treatable with an opioid agonist and further, that person of ordinary skill would be taught away from using noribogaine to treat neuropathic pain as taught by

Olney because of noribogaine's substantially reduced activity vis-à-vis the NMDA receptor, the target of the Olney disclosure. In sum, Olney clearly does not anticipate the present invention.

The Rejection of Claims 6-9 As Being Obvious Over Olney, GB '897 in view of Hussain

Separately, the Examiner newsley rejects claims 6-9 under 35 U.S.C. §103 as being obvious over Olney and GB 841,697 ("GB '697"), in view of Hussain, U.S. No. 4,464,378 ("Hussain"). The Examiner argues that Olney teaches the use of ibogaine to treat pain and that GB '697 discloses that ibogaine is an analgesic agent useful in an analgesic composition for treating or alleviating pain. The Examiner relies on Hussain for teaching that opioid antagonists such as naloxone, naltrexone and nalorphine are well known analgesics and therefore useful in a method of treating or alleviating pain in a patient. The Examiner also acknowledges that noribogaine was known as a metabolite of ibogaine.

From a combination of the above three references, the Examiner concludes that it would have been obvious to one or ordinary skill in the art to employ noribogaine in combination with an opioid antagonist such as nalozone, nalterone and nalorphine in a method to alleviate pain and to optimize the effective amounts of active agents in the composition. Applicants respectfully traverse the Examiner's arguments.

As amended, claims 6-9 are directed to the use of a combination of noribogaine and an opioid antagonist in claimed amounts or delivered transdermally to treat or alleviate pain which is otherwise treatable by an opioid agonist. A combination of Olney and GB '697 in view of Hussain, rather than rendering the present claims obvious, actually teaches away from the present invention.

Olney, discussed above, is directed to the use of ibogaine in the treatment of neuropathic pain by functioning as an antagonist of NMDA receptors. Olney specifically indicates in the abstract, as discussed above, that ibogaine is used to treat pain which is not treatable with an opioid agonist such as morphine. As explained above, this is because Olney discovered that ibogaine acts as an antagonist of NMDA receptors. The present specification, in the examples at page 9-10, as well as the prior art cited, recognized that ibogaine has virtually no activity as an analgesic agent to treat pain in the same manner as morphine. There

is no way to combine the references cited to render the present invention obvious.

None of the references teach that noribogaine has activity and is useful as a non-addictive analgesic agent to treat or alleviate pain treatable by an opioid agonist such as morphine. Olney doesn't even mention noribogaine, and actually teaches away from using ibogaine to treat pain mediated through μ receptors, through which opioid agonists and quite unexpectedly, noribogaine act to alleviate pain. GB '697 does not even recognize ibogaine as an analgesic agent and in particular confirms the teaching in Olney that ibogaine cannot be used to treat pain which is treatable using an opioid agonist.

GB '697 describes the use of a number of narcotic morphine analogs (including morphine) in combination with ibogaine or tabernanthine for analgesic use. GB '697 does not disclose noribogaine as an analgesic agent alone, and further only suggests the use of an addictive analgesic agent having morphine-like characteristics (i.e., an opioid analgesic) in combination with ibogaine or tabernanthine. This is not the present invention, which specifically uses noribogaine as a non-addictive analgesic (a receptor agonist) and avoids both ibogaine and addictive opioid receptor agonists such as morphine. In preferred embodiments of GB '697, as set forth in examples 1-2 5, 7-8 and 11, the use of morphine is described in combination with ibogaine or tabernanthine. This teaching is in complete contrast to the present invention inasmuch as the present invention relies on noribogaine as a *nonaddictive* analgesic acting *alone* in the first instance, and when combined with another agent, that agent is an opioid *antagonist*- i.e., an *opioid inhibitor*, not an opioid *agonist* such as morphine. A review of the instant claims shows that Applicant specifically has disclaimed any subject matter which might read on the teachings of GB '697. Note that the present methods are used in "the absence of an opioid analgesic", such as morphine or a related opioid agonist. Thus, GB '697 clearly does not teach the present invention, for it fails to teach or suggest noribogaine even obliquely, and when it discloses ibogaine, ibogaine is disclosed *in combination* with another agent, that agent being the addictive analgesic agent morphine, which is an opioid agonist, not an opioid *antagonist* as claimed. Note that GB '695 clearly indicates at page 2, column 1, lines 5-6 that the art recognized that ibogaine per se did not have analgesic activity- i.e., *activity as a receptor agonist*, the receptors and action through which morphine acts to alleviate pain. GB '697 clearly does not obviate the deficiencies of Olney in failing to disclose or suggest the present invention. To the extent that Olney and GB

'697 are combined, they provide no further enlightenment than GB '697 alone, i.e., that ibogaine may be used in combination with an addictive analgesic agent such as morphine, a combination which is clearly not the present invention and has been disclaimed.

Turning to Hussain, this reference completely fails to even disclose or suggest noribogaine and consequently, fails to disclose or suggest the present invention. In the present invention in claims 6-9, the use of noribogaine *in combination* with an opioid antagonist to treat pain treatable with an opioid agonist analgesic agent is claimed. None of Olney, GB '697 or Hussain teaches that noribogaine may be used as an analgesic to treat pain treatable by an opioid agonist, alone or in combination with an opioid antagonist. In fact, as set forth above, Olney teaches that ibogaine possesses no opioid analgesic activity, thus, the person of ordinary skill would not use ibogaine as an opioid analgesic. Hussain merely provides certain known compounds adapted for nasal administration, some of which are opioid agonists, some of which are opioid antagonists. Hussain does not obviate the deficiencies of Olney and GB '697. Moreover, the art does ***not*** recognize that opioid antagonists have analgesic activity, and it is respectfully submitted that opioid antagonists, such as naloxone and naltrexone, are not useful in the combination taught by GB '697, because they do not exhibit analgesic activity. That is precisely why naloxone and naltrexone are referred to in the art as opioid *antagonists*. Opioid *agonists* such as morphine, not *antagonists*, such as naloxone and naltrexone, are the agents which exhibit analgesic activity and this is precisely why GB '697 teaches a combination of ibogaine and an opioid agonist analgesic, a combination which is not claimed by the present invention. Moreover, Hussain does not even mention noribogaine or ibogaine. Consequently, none of these references alone or in combination teaches or suggests the present invention and the present invention is non-obvious over the disclosure of these references.[1]

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1 To the extent that the Examiner is somehow construing an obviouness argument based upon the view that naloxone and naltrexone, as taught by Hussain, can be combined with ibogaine as taught by GB '697 or Olney, to produce substantial non-addictive opioid analgesic activity because ibogaine, once in a patient's body will metabolize to noribogaine, that is simply not a cogent argument. As explained, the cited references actually *teach away* from such a combination. There is absolutely no suggestion in GB '697 that the use of ibogaine and an opioid antagonist would be an effective combination as an opioid analgesic and nothing in the art suggests that such a combination would be effective as an opioid analgesic given the clear teachings of Olney that ibogaine does not possess such activity and an opioid antagonist is generally known *not* to possess analgesic activity. Such a combination would be taught by the art not to work as an opioid analgesic.

The present invention relates to the unexpected discovery that noribogaine, in contrast to ibogaine, may be used as a *non-addictive* analgesic agent (i.e., noribogaine can be used to treat pain which is otherwise treatable using an addictive opioid agonist such as morphine in a patient *without addiction*), either *alone* or in combination with an opioid *antagonist* as a particularly effective non-addictive analgesic. Thus, the present invention makes use of noribogaine's unique activity and represents a particularly effective method for alleviating pain, an advance in the art and an exciting improvement over the treatments of the prior art, given the lack of addiction associated with noribogaine's use. Methods which make use of noribogaine in combination with an opioid antagonist represent alternative embodiments of the present invention. Note that noribogaine is particularly effective as an analgesic agent because it is a full *mu* opioid agonist, is particularly effective in this regard, and is also *non-addictive*, in contrast to the opioid analgesics, i.e., the opioid agonists, such as morphine and related compounds. In addition, in contrast to ibogaine which evidences activity against neuropathic pain by inhibiting NMDA receptors, noribogaine exhibits vastly superior analgesic activity for pain as an *agonist* of the receptor similar to the effect of morphine (in fact, ibogaine is known in the art as possessing ***no*** significant analgesic activity on its own similar to noribogaine as taught by Olney and this is further born out by the examples on page 9-10 of the instant specification). Moreover, noribogaine is free from the psychomimetic side effects of ibogaine, a deleterious side effect which limits ibogaine's use to treat unrelated (to the present invention) neuropathic pain.

In contrast to the Examiner's arguments, the present invention is clearly patentable and non-obvious over the teachings relied upon by the Examiner. It is respectfully submitted by Applicant that Olney and GB '697 do not and cannot teach or suggest the present invention, and that Hussain, by failing to even mention the present invention, does not obviate the gross deficiencies of Olney and GB '697. The combination of references cited against the instant application fails to render the presently claimed invention unpatentable.

For the above reasons, Applicant respectfully asserts that the claims set forth in the amendment to the application of the present invention are now in compliance with 35 U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited.

Applicants have not added or cancelled any of the previously presented claims in this paper. Applicants previously have cancelled 15 claims (two independent) in the present application. No fee is therefore due for the presentation of this amendment. A petition for a three month extension of time is enclosed as is the appropriate fee of $510 (small entity status applies). If any additional fee is due or any overpayment has been made, please charge/credit Deposit Account No. 04-0838. Should the Examiner wish to discuss the present application in an effort to advance its prosecution, the undersigned attorney may be reached at the telephone number set forth hereinbelow.

Respectfully submitted,
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Henry D. Coleman